Serum Concentrations of 1,1,1-Trichloro-2,2-bis (*p*-chlorophenyl)ethane (DDT) and 1,1-Dichloro-2,2-bis (*p*-chlorophenyl)ethylene (DDE) and Risk of Primary Liver Cancer

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Background: **1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) exposure has been demonstrated to cause liver tumors in laboratory rodents. DDT's persistent metabolite and environmental degradation product, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), has also been associated with liver tumors in laboratory animals. Whether DDT and DDE are associated with hepatocarcinogenesis in humans is not clear.** ***Methods:*** **We carried out a nested case–control study among the participants of the Nutritional Intervention Trials in Linxian, China. The case group included 168 individuals who developed liver cancer during the trials, and the control group included 385 individuals frequency-matched on age and sex who were alive and well at the end of the study. Serum concentrations of DDT and DDE were measured by gas chromatography–mass spectrometry. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable analysis.** ***Results:*** **In multivariable-adjusted models, the risk of developing liver cancer increased with increased serum DDT concentration (OR for quintile 1 versus quintile 5 = 3.8, 95% CI = 1.7 to 8.6, P_{trend} = .0024). In contrast, there was no statistically significant association between liver cancer and serum DDE concentration. The association between high serum DDT concentration and liver cancer was stronger among individuals with DDE concentrations below the median value (odds ratio for tertile 3 versus tertile 1 = 3.55, 95% CI = 1.45 to 8.74) than those with concentrations above the median (OR = 1.70, 95% CI = 0.97 to 2.98). A calculation of crude liver cancer risk found that there would be 26 liver cancers per 100 000 persons per year in the lowest quintile of DDT exposure versus 46 liver cancers per 100 000 persons per year in the highest quintile of DDT exposure.** ***Conclusions:*** **DDT may be a risk factor for liver cancer, particularly among persons with lower DDE concentrations. Risk may be particularly increased among persons exposed directly to DDT (resulting in a higher ratio of DDT to DDE) or, alternatively, risk may be associated with individual ability to metabolize DDT to DDE. [J Natl Cancer Inst 2006;98:1005–10]**

Primary liver cancer is the sixth most common cancer in the world, with more than 80% of the cases arising in developing countries. More than half of all liver cancer cases occur in China *(1)*, where it is the second most common cancer among men and the fourth most common among women *(2)*. In China, the dominant type of liver cancer is hepatocellular carcinoma. As in most other developing countries, the major established risk factors for hepatocellular carcinoma in China include chronic infection with hepatitis B virus (HBV), ingestion of aflatoxin B_1 (AFB_1) in contaminated foodstuffs, heavy alcohol consumption, and cirrhosis of the liver. Infection with hepatitis C virus (HCV) also contributes to the liver cancer burden, although the attributable risk in most countries in the developing world is considerably less (<10%) than that of HBV (60%) *(3)*. Even among persons at very high risk of liver cancer due to infection with HBV and AFB_1 exposure, however, only 20% will develop liver cancer. The reasons for the disparity in risk among similarly exposed persons are unclear, but unidentified risk factors and/or differences in genetic susceptibility may be responsible. Therefore, the identification of new risk factors may be important in understanding the etiology of liver cancer.

One new risk factor may be 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT). DDT was originally synthesized in 1874, although its insecticidal capability was not discovered until 1939 *(4)*. Used as an antimalarial agent by the military during World War II, DDT came into general commercial use at the end of the war and was the most widely used insecticide in the world until the mid-1960s *(5)*. By the early 1970s, however, DDT's long persistence in the environment and evidence of adverse reproductive effects among animals led many developed countries to ban the insecticide *(4)*. China banned the agricultural use of DDT in 1983 but is still producing the compound for malarial control and for use in dicofol production *(6)*.

An association between DDT and liver cancer has been suggested by both animal and human studies. Laboratory animals

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exposed to DDT show dose-related increases in liver tumors *(4)*. Humans exposed to DDT via their work as pesticide applicators have been reported to have increased rates of liver cancer *(7–8)*. Also, a recent ecologic study among white people in the United States reported a statistically significant correlation between levels of 1,1,dichloro-2,2, bis(*p*-chlorophenyl) ethylene (DDE; a metabolite of DDT) levels in adipose tissue and liver cancer mortality rates *(9)*. To date, however, there has not been a direct examination of DDT or DDE concentrations in body tissues and the risk of developing liver cancer among humans. Here we report the result of our examination of this question in a nested case–control study performed in Linxian, China.

Subjects and Methods

Study Design

Linxian, China, is an area with high incidence of squamous cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia *(10)*. To determine whether micronutrient supplementation could ameliorate the population's chronic deficiencies of multiple nutrients and decrease the incidence and mortality of these tumors, two nutritional intervention trials (the Dysplasia Trial and the General Population Trial) were conducted between March 1986 and May 1991 *(10)*. Both trials were randomized, double blind, and placebo controlled, and they tested the effect of multiple vitamin and mineral supplements. The Dysplasia Trial included 3318 individuals (56% female) with a cytologic diagnosis of esophageal dysplasia. The General Population Trial included 29 584 individuals (55% female) drawn from the general population of Linxian. All participants in both trials were between 40 and 69 years of age at enrollment and were residents of four northern Linxian communes (Yaocun, Rencun, Donggang, and Henshui). Baseline screening examinations were conducted in late 1984 and early 1985, before the intervention was started. At the baseline screening examination, a 10-mL blood sample was collected from each participant and frozen. Other than for cancers of the esophagus and gastric cardia, no other cancer screening was conducted at baseline. All participants provided written informed consent, and the trials were conducted in accordance with the U.S. Department of Health and Human Services Office for Protection from Research Risks guidelines.

Compared with the high-risk regions on the coast of China, liver cancer incidence is relatively low in Linxian, which is located in inland Henan Province. As of May 2001, 162 participants in the General Population Trial and 24 participants in the Dysplasia Trial had been diagnosed with liver cancer. Diagnosis was based on a variety of methods, including pathologic review, biochemical assays, clinical examination, ultrasound, and computed tomography scan. Of the 186 individuals who developed liver cancer during the study, serum samples remained from 168 individuals at the time the present analysis was conducted. Control subjects who had never been diagnosed with liver cancer were frequency matched to these 168 cases at a ratio of approximately 2 : 1 on age (within 2 years) and sex. A total of 385 control subjects were selected.

Questionnaire data concerning height, weight, smoking, drinking, family history of cancer, parity (among females), and residential water source were collected from all trial participants at baseline. Cigarette smoking was defined as a dichotomous variable, i.e., never- versus ever-smoking for at least 6 months. Because alcohol drinking was both uncommon and relatively light in the study population, alcohol consumption was also defined as a dichotomous variable, none versus any drinking in the previous 12 months. Residential running water was considered a dichotomous variable and coded as yes if the person had running water in the home and no if running water was not present. Family history of cancer was considered positive if a first-degree relative was reported to have had any cancer. Height and weight were analyzed as continuous variables. Among female participants, parity was analyzed as a continuous variable. The interval between blood draw and liver cancer diagnosis was defined as a categorical variable, with strata of 0–6 yrs, more than 6 to 10 years, and more than10 years.

Laboratory Assays

Serum markers of the presence of HBV and HCV were analyzed using enzyme immunoassays, following the directions provided by the manufacturers. The following kits were used: antibody to hepatitis C virus (anti-HCV) was analyzed using the ORTHO HCV version 3.0 enzyme-linked immunosorbent assay (ELISA) Test System from Ortho-Clinical Diagnostics, Raritan, NJ; hepatitis B surface antigen (HBsAg) was analyzed by enzyme immunoassay using the Bio-Rad Genetic Systems HBsAg EIA 3.0 kit of Bio-Rad Laboratories, Hercules, CA; and antibody to hepatitis B core antigen (anti-HBc) was analyzed by ELISA using the HBc (recombinant) ORTHO ELISA Test System of Ortho-Clinical Diagnostics. Serum concentrations of DDT (*p*, *p*′-DDT) and DDE (*p*, *p*′-DDE) were determined at L'Institut National de Santé Publique du Québec by using previously described methods *(11)*. In brief, *p*, *p*′-DDT and *p*, *p*′-DDE were extracted from serum by using solid-phase extraction (C_{18} column). After a washing step, *p*, *p*′-DDT and *p*, *p*′-DDE were eluted from the column with isooctane. The extracts were then analyzed by gas chromatography–mass spectrometry. For each series, in-house controls and standards (5 mg/L and 25 mg/L) were analyzed, in addition to blinded quality control samples included with the study samples. *p*, *p*′-DDE–^{13}C and *p*, *p*′-DDT–^{13}C were used as internal standards. The quantitation limit for both analytes was 0.5 mg/L, and the detection limit was 0.2 mg/L. The coefficient of variation for *p*, *p*′-DDT was 6.1%, and that for *p*, *p*′-DDE was 7.1%. To verify accuracy of the DDT and DDE measurements, the laboratory successfully participates in the German External Quality Assessment Scheme organized by the University of Erlangen–Nuremberg (http://www.g-euqas.de).

Total serum lipid levels were estimated from measurements of free cholesterol (FC) and total cholesterol, phospholipids, and triglycerides. Estimates of total serum lipid levels were calculated by adding the individual lipid components by the formula: total serum lipid levels = 1.677 (total cholesterol − FC) + FC + triglycerides + 0.623 *(12)*. All data are presented as nanograms of DDT or DDE per gram of lipid (ng DDT/g lipid or ng DDE/g lipid).

Statistical Analysis

Participant data were tabulated by case–control status, and unadjusted comparisons were made using *t* tests for continuous variables and chi-square tests for categorical variables. The correlation between lipid-adjusted DDT and DDE was calculated using Spearman rank correlation. Multivariable linear regression was employed to examine the relationships between DDT and

DDE and possible predictors of their status. Variables found to predict the status of either DDT or DDE were then adjusted for in logistic regression models that examined the relationship between DDT and DDE and liver cancer. DDT and DDE quintiles and DDT tertiles were calculated based on the distribution among control subjects. The associations between serum concentrations of DDT and DDE and cancer risk were estimated using multivariable logistic regression models. In addition to the strata of DDT and DDE concentrations, the models included terms for age, sex, commune of residence, and HBsAg status. *P* values from logistic regression models were calculated using likelihood-ratio tests. To examine possible interactions among DDT and DDE, the logistic regression model was fit with adjusting covariates, the DDE median split, five DDT strata, and DDT quintile indicators × the DDE median split to render a 4-degree-of-freedom test. All tests were two-sided, and *P* values less than or equal to .05 were considered statistically significant. Statistical analyses were conducted using SAS statistical software version 9.0 (SAS Institute, Cary, NC). Absolute risks were estimated using the methodology of Mark and Katki *(13)* and computed with the NestedCohort package in R *(14)*.

Results

Characteristics of the study population are presented in Table 1. There were no statistically significant differences between the case patients and control subjects in any of the following characteristics: age, sex, height, weight, body mass index (weight in kilograms divided by square of height in meters), smoking status, drinking status, parity (among women), family history of cancer, living in a home with running water, commune of residence (shown as communes 1–4 to preserve confidentiality), or trial participation (Dysplasia Trial versus General Population Trial). Similarly, there was no difference between case patients and control subjects in the percentage of participants who were positive for antibody to HCV (8%). The case and control groups did differ with respect to HBV infection status, however, with case patients being statistically significantly more likely than control subjects to be anti-HBc positive (*P* = .0018) and to be HBsAg positive (*P*<.001).

There were no statistically significant differences between the case patients and control subjects in the lipid-adjusted geometric mean values of DDT and DDE (Table 1). Similarly, the DDT distributions of the case and control subjects did not differ when the data were categorized into quintiles based on the distribution in the control group (*P* = .71). The DDE distributions, however, were statistically significantly different (*P* = .007), with the values of the case subjects more likely to cluster in the middle of the distribution than at either end.

The relationships between the study covariates and lipid-adjusted serum DDT and DDE concentrations were examined using a single multivariable model for each log-transformed analyte (Table 2). Older age (i.e., >50 years) and commune of residence were both statistically significantly related to DDT level. Older age, commune of residence, and male sex were related to DDE level. Smoking, drinking, height, weight, parity (among women), residential running water, interval between blood draw and cancer diagnosis, and chronic infection with either HBV or HCV were unrelated to either DDT or DDE level. As anticipated, DDT and DDE levels were statistically significantly correlated with one another ($r = 0.6$, $P = .02$).

Table 1. Characteristics of the study population*

Characteristic	Case patients	Control subjects	*P*†
No.	168	385	
Age, mean (SD)	55.8 (8.1)	55.3 (8.0)	.49
Male sex	117 (70%)	264 (69%)	.80
Height, mean (SD)	1.61 (0.07)	1.60 (0.08)	.79
Weight, mean (SD)	56.2 (7.0)	55.6 (7.4)	.40
BMI (kg/m^2), mean (SD)	21.8 (2.1)	21.6 (2.1)	.35
Ever smoker for at least 6 mo	80 (48%)	177 (46%)	.72
Any drinking in last 12 mo	42 (25%)	108 (28%)	.46
Parity (women only), mean (SD)	4.6 (1.7)	4.4 (1.6)	.27
Family history of any cancer† (yes)	72 (43%)	135 (35%)	.082
Running water in residence (yes)	133 (79%)	291 (76%)	.36
Trial			
General Population Trial	149 (89%)	334 (87%)	.53
Dysplasia Trial	19 (11%)	51 (13%)	
Commune			
1	71 (42%)	134 (35%)	.16
2	26 (15%)	89 (23%)	
3	36 (21%)	87 (23%)	
4	35 (21%)	75 (19%)	
Hepatitis viral markers			
anti-HBc(+)	118 (70%)	216 (56%)	.0018
HBsAg(+)	42 (25%)	15 (4%)	<.0001
anti-HCV(+)	13 (8%)	31 (8%)	.90
DDT‡ (ng/g of lipid), quintile			
1 (<265)	26 (15%)	77 (20%)	.71
2 (265–382)	35 (21%)	77 (20%)	
3 (383–521)	34 (20%)	77 (20%)	
4 (522–787)	33 (20%)	77 (20%)	
5 (>787)	40 (24%)	77 (20%)	
DDE§ (ng/g lipid), quintile			
1 (<1767)	27 (16%)	77 (20%)	.007
2 (1767–2443)	27 (16%)	77 (20%)	
3 (2444–3478)	48 (29%)	77 (20%)	
4 (3479–5458)	47 (28%)	77 (20%)	
5 (>5458)	19 (11%)	77 (20%)	

*SD = standard deviation; BMI = body mass index; anti-HBc = antibody to hepatitis B core antigen; HBsAg = hepatitis B surface antigen; anti-HCV = antibody to hepatitis C virus; DDE = 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane; DDT = 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane.

†All *P* values are two-sided and are based on *t* tests for continuous variables and chi-square tests for categorical variables. All tests had 1 degree of freedom except commune, which had 3. The *t* tests for DDT and DDE were calculated using log-transformed data.

‡The geometric mean of DDT was 487 ng/g lipid in the case subjects and 490 ng/g lipid in the control subjects (*P* = .97).

§The geometric mean of DDE was 2931 ng/g lipid in the case subjects and 2957 ng/g lipid in the control subjects (*P* = .88).

Using multivariable logistic regression models, we examined the association between quintile of each analyte and liver cancer, while adjusting for the other analyte as a categorical variable. The DDT analysis, adjusted for age, sex, HBsAg, commune, and DDE level, found a statistically significantly increased risk of liver cancer among individuals with values in the highest versus the lowest quintile of serum DDT concentration (odds ratio [OR] = 3.8, 95% confidence interval [CI] = 1.7 to 8.6), with evidence of a linear trend with increasing DDT concentration (*P* = .0024) (Table 3). A calculation of crude liver cancer risk found that there would be 26 liver cancers per 100 000 persons per year in the lowest quintile of DDT exposure versus 46 liver cancers per 100 000 persons per year in the highest quintile of DDT exposure. In contrast, although individuals in the fourth DDE quintile had a statistically significantly higher risk than those in the first DDE quintile (OR = 1.9, 95% CI = 1.0 to 3.1), there was no evidence of a linear trend in risk with increasing quintile of DDE concentration (*P* = .51).

Table 2. Predictors of lipid-adjusted serum DDT and DDE concentration among all participants from multivariable linear regression models*

Characteristic	DDT		DDE	
	β coefficient	*P*	β coefficient	*P*
Intercept†	−0.74	.32	0.49	.49
Age, y				
<50	Referent		Referent	
50–59	0.15	.023	0.24	.0002
>60	0.24	.0010	0.42	<.0001
Height (cm)	0.090	.10	0.14	.0080
Weight (kg)	−0.0030	.55	−0.011	.0178
Sex				
Female	Referent		Referent	
Male	−0.18	.033	0.23	.0040
Ever smoker (at least 6 mo)				
No	Referent		Referent	
Yes	0.077	.27	0.057	.38
Any drinking in last 12 mo				
No	Referent		Referent	
Yes	0.025	.68	0.031	.56
Running water				
No	Referent		Referent	
Yes	−0.015	.82	−0.017	.79
Commune				
1	Referent		Referent	
2	0.82	<.0001	0.40	<.0001
3	0.23	.0017	0.15	.0034
4	0.51	<.0001	0.51	<.0001
HBsAg				
Negative	Referent		Referent	
Positive	0.070	.20	0.036	.49
Anti-HCV				
Negative	Referent		Referent	
Positive	−0.16	.11	−0.074	.43
Parity (women only)	−0.063	.032	−0.088	.0027
Time since diagnosis (case subjects only), y				
0–6	Referent		Referent	
>6–10	−0.0045	.96	0.021	.49
>10	−0.084	.43	0.079	.46

*DDE = 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane; DDT = 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; HBsAg = hepatitis B surface antigen; anti-HCV = antibody to hepatitis C virus. A single multivariable model was fitted using the log of the lipid-adjusted serum concentrations for DDT or DDE separately for all variables through HCV. Separate models were fitted for number of children (women only) and time to diagnosis (cases only) that included all variables in the main multivariable model.

†The intercept is the mean value predicted by the regression model, of either DDT or DDE, when all covariates equal zero or the reference level.

Using DDT quintiles and two categories of DDE (based on the median value), we examined an interaction between DDT and DDE concentrations and the risk of liver cancer. A global 4-degree-of-freedom test for interaction yielded a *P* value of .042. We next partitioned the data into 10 groups by using DDT quintiles that were divided at the median value of DDE. However, because the cell counts were small cell, we recategorized DDT into tertiles for this analysis. Individuals whose DDT levels were in the highest tertile were at statistically significantly increased risk of liver cancer (OR = 3.55, 95% CI = 1.45 to 8.74) if their DDE levels were below the median DDE concentration of 2961 ng/g lipid (Table 4). In contrast, the odds ratio for individuals in the highest tertile of DDT but with DDE levels above the median was lower, and the association did not attain statistical significance (OR = 1.70, 95% CI = 0.97 to 2.98).

Stratification of the analyses on HBV and HCV status found that the results for DDT and DDE did not differ between persons who were infected and persons who were not infected (data not shown). That is, the results were not confounded by viral infection and there was no evidence of interaction between viral infection and case status (data not shown).

Discussion

In this study, we found an increased risk of liver cancer in association with high levels of DDT. The risk was most pronounced among individuals with high DDT levels and low DDE levels. The association is consistent with findings among laboratory animals that indicate that, other than the nervous system, the liver is the only other organ affected by DDT. In most species, large doses of DDT cause focal hepatic necrosis *(4)*. Among rodents, DDT induces microsomal mixed-function oxidases and causes fat accumulation in the liver *(15–16)*. Among rodents fed DDT and DDE, liver tumors have developed *(17–18)*. Animal studies indicate that nutritional status affects the toxicity of DDT, such that undernutrition is associated with increased toxicity *(19)*. On the basis of the animal data, DDT has been classified as a possible human carcinogen by the International Agency for Research on Cancer and as a reasonably anticipated human carcinogen by the U.S. National Toxicology Program *(20–21)*.

Why there would be an association between DDT and liver cancer specifically when DDE levels are low is not clear. It is possible that direct exposure to DDT is critical to increasing the risk of liver cancer in that a higher ratio of DDT to DDE is thought to reflect more recent DDT exposure *(22)*. Over time, degradation of DDT to DDE in the environment results in a lower ratio of DDT to DDE and is consistent with DDT exposure having occurred in the past. Also, the risk associated with higher

Table 3. Adjusted odds ratios and 95% confidence intervals for the association between incident liver cancer and serum DDT and DDE concentrations*

Analyte	Model	OR (95% CI)					
		Q1	Q2	Q3	Q4	Q5	P_{trend}
DDT	Crude	Referent	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.4)	1.3 (0.7 to 2.3)	1.5 (0.9 to 2.8)	.24
	Adjusted†	Referent	1.3 (0.7 to 2.5)	1.4 (0.7 to 2.6)	1.4 (0.7 to 2.7)	2.0 (1.1 to 3.9)	.049
	Adjusted with DDE‡	Referent	1.5 (0.8 to 2.7)	1.7 (0.9 to 3.3)	2.1 (1.0 to 4.3)	3.8 (1.7 to 8.6)	.0024
DDE	Crude	Referent	1.0 (0.5 to 1.9)	1.8 (1.0 to 3.1)	1.7 (1.0 to 3.1)	0.7 (0.4 to 1.4)	.85
	Adjusted†	Referent	1.0 (0.5 to 1.9)	1.7 (0.9 to 3.0)	1.8 (1.0 to 3.3)	0.7 (0.3 to 1.5)	.75
	Adjusted with DDT‡	Referent	1.0 (0.5 to 1.9)	1.7 (0.9 to 3.1)	1.9 (1.0 to 3.1)	0.8 (0.3 to 1.7)	.51

*DDE = 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane; DDT = 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane; OR = odds ratio; CI = confidence interval; Q = quintile.

†Adjusted odds ratios and 95% confidence intervals come from logistic regression models that included age, sex, HBsAg status, and commune of residence.

‡Mutually adjusted for either continuous DDE or continuous DDT.

Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between liver cancer and serum DDT concentration by DDE stratum*

DDE stratum	DDT tertile		
	≤331 ng/g	>331 to <581 ng/g	≥581 ng/g
Below median (<2961 ng/g lipid)			
Control subjects : Case subjects	116 : 36	61 : 29	15 : 12
OR (95% CI)	1.00 (Referent)	1.69 (0.93 to 3.09)	3.55 (1.45 to 8.74)
At or above median (≥2961 ng/g lipid)			
Control subjects : Case subjects	12 : 7	68 : 35	113 : 49
OR (95% CI)	1.70 (0.61 to 4.77)	1.74 (0.97 to 2.98)	1.70 (0.97 to 2.98)

*DDE = 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane; DDT = 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane. Odds ratios and 95% confidence intervals come from logistic regression models that included age, sex, HBsAg status, and commune of residence.

DDT and lower DDE may reflect genetic differences in capacity to metabolize DDT. Early studies of DDT metabolism in humans, for example, reported striking interpersonal differences in the decline of DDT levels in adipose tissue *(23)*. Which specific genetic loci are associated with DDT conversion requires more study, although it has been suggested that African Americans have higher serum levels of DDT than white Americans because of polymorphisms in the glucose-6-phosphate dehydrogenase gene *(24)*. More research concerning genetic control of DDT metabolism may help to answer this question.

Few epidemiologic studies of DDT and liver cancer have been conducted among humans. Two Italian studies of insecticide applicators with occupational exposure to DDT reported statistically significantly increased risks of liver and biliary tract cancers *(7–8)*, although a more extensive examination of the latter study population did not confirm an increased risk *(25)*. Also, an ecologic study in the United States reported a statistically significant association between mean adipose DDE levels and liver cancer mortality among white persons *(9)*. In contrast to these reports, a Swedish study that interviewed relatives of deceased cases and control subjects reported no association between DDT exposure and liver cancer *(26)*. Similarly, an occupational study of long-term DDT exposure reported no liver disease among the 31 participants *(27)*. Autopsy studies have reported evidence of higher DDT levels among persons who died of cirrhosis *(28–29)* but have differed as to whether the higher levels were the result of fatty infiltration of the liver. Although the induction of microsomal hepatic enzymes by DDT is known to cause morphologic changes in rodent livers, it has been argued that the level of exposure required for such changes far exceeds that of the general human population *(4)*.

An association between DDT/DDE and liver cancer has not been observed in all epidemiologic studies. The lack of association in other studies may reflect the fact that they did not measure tissue concentrations directly but relied on questionnaire data *(26)* or occupational records of exposure *(18)*. Most studies have also been relatively small, so they may not have had adequate statistical power to detect a fairly rare outcome *(26–27)*. Another possible reason that a liver cancer association was found in this study is that the DDT and DDE levels are higher in China than in Western countries *(22,30)*. For example, whereas the median DDT levels in this study were 490 ng/g of lipid, median levels have been previously reported to be 12.6 ng/g of lipid in Canada and 29.4 ng/g of lipid in Sweden *(22)*. DDT use in agriculture was banned in China in 1983 *(6)*, only 2 years before the collection of blood samples in this study. DDT has continued to be produced in China, however, for manufacture of dicofol, a nonsystemic acaricide, and for use in residential spraying in antimalarial campaigns *(31)*. Recent evidence indicates that DDT-contaminated dicofol could be associated with the continued higher concentrations of DDT in China *(6)*.

Finally, another possible explanation for why the association is detectable in Linxian may be that the population is notably undernourished. The diet is deficient in a wide range of nutrients, including riboflavin, retinol, α- and β-carotene, ascorbic acid, α-tocopherol, zinc, and molybdenum *(32–33)*, and some of these nutrient deficiencies have been prominently linked to the risk of esophageal and gastric cancers in Linxian *(34–36)*. Because animal experiments have shown a closer association between DDT and liver cancer in poorly nourished animals *(4)*, it is possible that DDT is also particularly carcinogenic in humans who suffer from malnutrition.

The study had several limitations, one being that not all liver tumors were histologically diagnosed. The possible inclusion of non–liver cancer cases in the case group however, would serve to dilute any association, thus indicating that the observed association may be stronger than we report here. Also, inadequate serum was available to determine whether the participants had evidence of exposure to AFB_1. However, although AFB_1 is a known risk factor for liver cancer in many underdeveloped countries, previous research has reported low levels of AFB_1 in Linxian *(37)*.

A major strength of this study was its prospective design. DDT and DDE levels were determined in prediagnostic serum samples and thus were not likely to be altered by the disease process or treatment. Also, questionnaire information on study covariates was obtained prior to diagnosis of cancer. Another strength of this study was that other well-known risk factors, including HBV, HCV, and alcohol consumption, were examined; they were found not to affect the relationship between DDT or DDE and liver cancer.

These findings indicate that DDT exposure may be risk factors for liver cancer in humans, especially in populations that are directly exposed to DDT, rather than just exposed to its metabolites. Comparison of the crude incidence in the lowest and highest quintiles of DDT exposure suggested that liver cancer incidence might be increased by 77% in populations with high exposure. On the basis of these observations, future research in the area of pesticide exposure and liver cancer should be encouraged.

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Notes

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